Add the following new claims:

36. (new) The method of claim 16, wherein

X_1 is from zero to six amino acids, and

X_2 is from zero to six amino acids.

37. (new) The method of claim 16, wherein X is selected from the group consisting of Ala, Leu, Ile, Val, Pro, Phe, Trp, Met, Ser, Thr, Tyr, Asn, Gln, Cys and Gly.

38. (new) The method of claim 37 wherein X is Asn, Phe, or His.

39. (new) The method of claim 16, wherein

X_1 is

(i) zero amino acids, or

(ii) the segment His-Gly-His-Glu-Gln-Gln-His-Gly-Leu-Gly-His-Gly (SEQ ID NO:1), or an N-terminal truncation fragment thereof containing at least one amino acid, and

X_2 is

(i) zero amino acids, or

(ii) the segment Leu-Asp-Asp-Asp-Leu-Glu-His-Gln-Gly-Gly-His-Val (SEQ. ID NO:2), or a C-terminal truncation fragment thereof containing at least one amino acid.

40. (new) The method of claim 39 wherein X is Asn, Phe or His.

41. (new) The method of claim 16, wherein the compound has at least about 30% amino acid sequence homology to the amino acid sequence His-Gly-His-Glu-Gln-Gln-His-Gly-Leu-Gly-His-Gly-His-Lys-Phe-Lys-Leu-Asp-Asp-Asp-Leu-Glu-His-Gln-Gly-Gly-His-Val (SEQ ID NO:5).

42. (new) The method of claim 16, wherein the compound has the amino acid sequence His-Gly-His-Glu-Gln-Gln-His-Gly-Leu-Gly-His-Gly-His-Lys-Phe-Lys-Leu-Asp-Asp-Asp-Leu-Glu-His-Gln-Gly-Gly-His-Val (SEQ ID NO:5).

43. (new) The method of claim 16, wherein the compound has the amino acid sequence Gly-His-Lys-Phe-Lys-Leu-Asp-Asp-Asp-Leu-Glu-His-Gln-Gly-Gly-His (SEQ ID NO:7).

44. (new) The method of claim 16, wherein

X_1 is

(i) zero amino acids, or

(ii) the segment Gly-His-Lys-His-Lys-His-Gly-His-Gly-His-Gly-Lys (SEQ ID NO:3) or an N-terminal truncation fragment thereof containing at least one amino acid, and

X_2 is

(i) zero amino acids, or

(ii) the segment Gly-Lys-Lys-Asn-Gly-Lys-His-Asn-Gly-Trp-Lys-Thr (SEQ ID NO:4) or a C-terminal truncation fragment thereof containing at least one amino acid.

45. (new) The method of claim 44 wherein X is Asn, Phe, or His.

46. (new) The method of claim 44, wherein the compound has at least about 30% amino acid sequence homology to the amino acid sequence Gly-His-Lys-His-Lys-His-Gly-His-Gly-His-Gly-Lys-His-Lys-Asn-Lys-Gly-Lys-Lys-Asn-Gly-Lys-His-Asn-Gly-Trp-Lys-Thr (SEQ ID NO:6).

47. (new) The method of claim 44, wherein the compound has the amino acid sequence Gly-His-Lys-His-Lys-His-Gly-His-Gly-His-Gly-Lys-His-Lys-Asn-Lys-Gly-Lys-Lys-Asn-Gly-Lys-His-Asn-Gly-Trp-Lys-Thr (SEQ ID NO:6).

48. (new) The method of claim 44, wherein the compound has the amino acid sequence Lys-His-Gly-His-Gly-His-Gly-Lys-His-Lys-Asn-Lys-Gly-Lys-Lys-Asn (SEQ ID NO:8).

49. (new) The method of claim 44, wherein the compound has the amino acid sequence His-Lys-Asn-Lys-Gly-Lys-Lys-Asn-Gly-Lys-His-Asn-Gly-Trp-Lys-Thr (SEQ ID NO:9)

Remarks

Claims 1-4, 8-9, 16, 19, 22, and 30-49 are pending in the application. Reconsideration is requested in view of the above changes and the following remarks.

The claims of non-elected Groups II and II (17, 18, 20, and 23-29), have been cancelled without prejudice to the filing of a divisional application. Reconsideration of the restriction requirement is requested to the extent claims 30-35 are grouped in Group II. The restriction requirement has alleged that these claims are among the claims "drawn to a method of inhibiting endothelial cell proliferation". This is incorrect. Claims 30-35 are directed to compounds per se and are properly grouped in elected Group I. Claims 30-35 are directed to compounds contained in the pharmaceutical compositions of Group I. Rejoinder of claim 30-35 into elected Group I is earnestly solicited.

The specification has been amended in the description of the figures to conform with the shading in the figures. An obvious error has also been corrected in the formula at page 20. In the denominator of the equation, the first occurrence of "(-GF)" should be "(+GF)." As written, the denominator would be 0, which is impossible.

The amendment to claim 1 is supported by original claim 5, now cancelled. New claims 36-49 are supported by original claims 1-15, and the specification.

Response to rejections under 35 U.S.C. § 112 (2)

Under this provision, the examiner's action rejects all pending claims: Claims 1-16, 19 and 22. However, the office action describes and gives rational bases only for the rejections to claims 1 through 16. The examiner's action does not state the reason for the rejection of claims 19 and 22. In effect, the office action states no rejection for claims 19 and 22 and applicant has not been apprised why claims 19 and 22 have been rejected. Since the applicant cannot respond to unexpressed rejections, applicant requests a formal correction that the office action does not reject claims 19 and 22 under 35 U.S.C. §112(2).

Claim 1 was rejected for reciting "and/or". The language has been removed from claim 1, and also from claim 30.

Claim 16 has been rejected as indefinite on the basis of the indefinite article ("administering...a composition according to claim 1), instead of ""administering...the composition according to claim 1. The rejection has been rendered moot since claim 16 is now independent.

Claim 1 was rejected for alleged indefiniteness with respect to the elements X, X_1 and X_2, each of which may be substituted by a different group of amino acids. The examiner avers that "it is unclear as to the effect of 1-12 additional amino acids in the positions of X_1 and X_2 on the activity of the compound versus having zero amino acids in those positions". The examiner also avers that "it is unclear what effect any amino acid at position X will have on the activity of the claimed compound."

The examiner's action with respect to claims 1 has not set forth a *prima facie* rejection under 35 U.S.C. §112, second paragraph. Under 35 U.S.C. §112, second paragraph, the claims "must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant." MPEP §2171. The Patent Office evaluates this objective requirement by

determining whether the claim language is indefinite. To so determine, "[a]pplicants are required to make clear and precise the terms that are used to define the invention whereby the metes and bounds of the claimed invention can be ascertained". MPEP §2173.05(a). However, perfect clarity of meaning and precision of communication are not required as "acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification". MPEP §2173.05(b). Essentially, a §112, second paragraph rejection seeks to identify and correct ambiguity of claim language or grammatical structure so that the recited scope of the invention is clear to one skilled in the art. A §112, second paragraph rejection is never properly directed to the substance of the claimed invention, but to the linguistic form of the claim. Examiner's objection is directed to the substance of the invention.

Element X is precisely defined as being one of any of the amino acids; elements X_1 and X_2 are specifically recited segments of amino acids or precisely defined truncated fragments of these segments having at least one amino acid. The examiner's statements ("it is unclear as to the effect of 1-12 additional amino acids in the positions of X_1 and X_2 on the activity of the compound versus having zero amino acids in those positions" and "it is unclear what effect any amino acid at position X will have on the activity of the claimed compound") raise a concern not about unclear language, improper antecedence or ambiguous meaning but about the activity of the recited compound, in other words, the substance of the claimed subject matter. Such a concern over substance is not the proper domain of a §112, second paragraph rejection. The examiner has not stated a *prima facie* rejection under this provision as to claim 1 and applicant requests the rejection be withdrawn.

Claims 7 and 12 were rejected for reciting the phrase "substantial amino acid sequence homology" which the specification defines in a manner that the examiner finds indefinite. The claims have been cancelled.

Response to Rejections under 35 U.S.C. §102

Response to Rejection over Halazonetis et al.

The examiner rejected claims 1-3, 5, 7-10, 12-15 as being anticipated by WO 96/25434 and U.S. Pat. No. 6,245,886 (collectively "Halazonetis et al.").

The MPEP at §2131 states that " '[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' (citations omitted)." X_1 as defined in amended claim 1 must always contain at a minimum the amino acid Glycine (Gly) in the N-terminal direction adjacent the core sequence His-Lsys-X-Lys.

Halazonetis et al., in pertinent part, discloses the amino acid sequence His-Lys-Ser-Lys-Lys (SEQ ID NO. 21). It can be readily appreciated that the Halazonetis et al. SEQ ID NO: 21 does not set forth each and every element of the minimum sequence of amended claim 1 since it lacks the glycine residue of the claimed core sequence Gly-His-Lsys-X-Lys.

Claims 2-4, 8 and 9 depend from claim 1 and recited additional features thereof. Since claim 1 is not anticipated by the asserted reference, neither are these additional claims.

As Halazonetis et al. does not recite each and every element of the claimed invention, applicant requests the withdrawal of the rejections relating to these references.

Response to Rejection over Ferreira et al.

Claims 1-15 have been rejected as being allegedly anticipated by Ferreira et al. WO 97/05258 under 35 U.S.C. §102(b), citing that Ferreira et al. at page 74 discloses amino acid sequence Glu-Ala-Pro-His-Lys-Phe-Lys-Asn-Val (as SEQ ID NO:113). Amended claim 1 recites at a minimum the following amino acid sequence: **Gly**-His-Lys-X-Lys. Because X_1 must always contain at least the amino acid Glycine (Gly), and because Ferreira et al. does not disclose Gly in the N-terminal position immediately preceding the claimed core sequence, Ferreira et al. does not anticipate claim 1 as amended.

Response to Rejection under 35 U.S.C. §103(a)

Claims 1-3, 5, 7-10, 16, 19 and 22 have been rejected as being allegedly obvious over the '886 patent to Halazonetis et al. in view of Wachtfogel et al., 269 J. Biol. Chem. 19307 (1994).

With respect to the rejection of claim 1, Wachtfogel et al. fails to remedy the deficiencies of Halazonetis et al. The former merely reports research results that identify domains of HK which bind to neutrophils. Wachtfogel et al. does not disclose any peptides relevant to the peptides of the claim 1 composition. Wachtfogel et al. does not provide any teaching or motivation for adding an N-terminal glycine residue to the SEQ ID NO. 21 peptide of Halazonetis et al. The resultant of the asserted combination is not the invention of claim 1. Claim 1, and claims 2, 3, 8 and 9 depending therefrom, are not obvious over the asserted references.

Claim 16 is directed to a method of treating angiogenesis with a composition containing the peptide X_1-His-Lys-X-Lys-X_2. Halazonetis et al. does not teach a method of inhibiting angiogenesis. The reference does not relate to kininogen or to its peptide segments but to peptide segments of the p53 protein, which is a DNA-binding protein having tumor suppressor function. The peptide His-Lys-Ser-Lys-Lys (SEQ ID NO. 21), described by Halazonetis et al. as an analog of a p53 fragment, is not disclosed as having any relevance to HK or angiogenesis. It is only by shear coincidence that SEQ ID NO:21 is subsumed in the amino acid sequence of HK domain 5.

Applicant has found that certain peptides based upon HMWK domain 5 are useful for inhibition of angiogenesis. Examiner acknowledges that Halazonetis et al. does "not explicitly teach a method of inhibiting angiogenesis". Notwithstanding, Examiner contends that the claimed method of inhibiting angiogenesis would be obvious over the combination of Halazonetis et al. and Wachtfogel et al. The latter does not remedy the deficiencies of the former.

Halazonetis et al. teaches peptides corresponding to a region of the human p53 protein, spanning residues 360-386, which negatively regulates DNA binding. The peptides are alleged to interfere with the function of this negative regulatory region (NRR1), and thereby activating p53's ability to bind DNA. Such activation is alleged to provide certain benefits, including enhancement of p53 function of abnormally proliferation cells, such as those associated with cancer, psoriasis, etc., thereby purportedly leading to treatment by apoptosis or growth arrest of such cells (col. 4 - col. 5).

Examiner characterizes Wachtfogel et al. as teaching: (1)"(HK) binds specifically to neutrophils and also inhibits the binding of fibrinogen to neutrophils"; and (2) "HK inhibits the binding of thrombin to platelets and endothelial cells". Examiner further characterizes Wachtfogel et al. as teaching "*inhibition of endothelial cells*, thrombin binding to platelets and that HK is involved in binding of neutrophils and the binding of fibrinogen". Examiner alleges that the claimed invention is obvious in view of the fact that migrating endothelial cells are known to form sprouts which form new blood vessels, coupled with Halazonetis et al. Examiner alleges that, "absent evidence to the contrary, angiogenesis is inhibited by the method taught by Wachtfogel et al. because the references (sic) demonstrate the inhibition of endothelial cells by HK".

No "method", therapeutic or otherwise, is taught by Wachtfogel et al. Those authors set out to map the HK binding site on neutrophils. The result of that research demonstrates that (1) the HK binding site on neutrophils is the MAc-1 antigen, (2) HK binds to Mac-1 via the HK D3 and D5 chains, and (3) HK's binding site on Mac-1 overlaps with the Mac-1 binding site for fibrinogen (because HK binding to neutrophils was blocked by fibrinogen), and (4) HK's binding site on Mac-1 is different from the Mac-1 binding site for factor X (because HK binding to neutrophils was not blocked by factor X peptides). No therapeutic use of HK, or any HK peptide, is taught or suggested by Wachtfogel et al.

Moreover, there is no teaching whatsoever in the four corners of Wachtfogel et al. of "inhibition of endothelial cells by HK". What property of endothelial cells

is being allegedly inhibited by HK? There is no teaching of any inhibitory effect of HK on any property of endothelial cells anywhere within the disclosure of Wachtfogel et al. The sole disclosure of HK interaction with endothelial cells by Wachtfogel et al. is contained at page 19307, col. 2, 2nd paragraph:

"Indirect evidence suggested that both the heavy chain (3) and the LC (6) are required for binding of HK to endothelial cells, and a recent study (12) provides direct evidence that either the LC or LK, which contains only the heavy chain, can displace HK from endothelial cells."

These statements reveal only that HK binds to endothelial cells. No inhibitory effect of HK on any property of endothelial cells is apparent from the disclosure of Wachtfogel et al. There is no basis for Examiner's finding that Wachtfogel et al. teach "inhibition of endothelial cells" by HK or any other molecule. There is certainly no basis for Examiner's bold pronouncement that angiogenesis is inhibited by any "method" taught by Wachtfogel" et al. Indeed no "methods" are taught. There is no basis in fact for finding the claimed invention obvious.

The fact that HK is known to bind neutrophils and also reciprocally inhibit the binding of fibrinogen to neutrophils (as stated in the first sentence of the Wachtfogel et al abstract) is completely irrelevant to whether or not HK, or any peptide of HK, can or will function as an anti-angiogenesis agent. Examiner has not explained the connection between HK inhibition of fibrinogen binding to neutrophils on the one hand, and angiogenesis on the other hand.

The fact that HK inhibits the binding of thrombin to platelets (as stated by Wachtfogel et al at col. 2, page 19307) is also irrelevant to a consideration of whether or not HK, or any peptide thereof, can or will function as an anti-angiogenesis agent. Examiner has not explained the connection between HK inhibition of thrombin binding to neutrophils and angiogenesis.

Finally, the allegation that Wachtfogel et al teach that HK inhibits the binding of thrombin to endothelial cells is incorrect (no such teaching can be

found in the reference). Even if true, it is not seen how this phenomenon is relevant to whether HK, or any peptide thereof, can or will function as an anti-angiogenesis agent.

The deficiencies of the primary reference, Halazonetis et al., are not remedied by the purported combination with Wachtfogel et al. First, there is not motivation or incentive whatsoever to combine the references. Halazonetis et al. teach peptides derived from human p53, a tumor suppressor protein. The Wachtfogel et al. paper is directed to localization of the HK binding site on neutrophils. The two disclosure have no relevance to one another, apart from the entirely fortuitous circumstance that Halazonetis et al.'s peptide SEQ ID NO:21, derived from the NRR1 domain of p53, mimics an amino acid sequence contained in domain 5 of an entirely unrelated protein, human high molecular weight kininogen. One skilled in the art would not make this most tenuous of connections. Even if one were to recognize the sequence overlap, there is not rational way one would ascribe any therapeutic significance thereto, let alone arrive at the claimed invention.

The invention of claim 16, directed to a method of inhibiting angiogenesis using specific peptides derived from HK domain 5, would not have been obvious to one of ordinary skill in the art in view of the disparate disclosures of Halazonetis et al. and Wachtfogel et al. Claim 16, and claims 36-49 depending therefrom, are patentable over the asserted references.

Claims 19 and 22 are directed to a method of inhibiting angiogenesis by administering an effective amount of two-chain or one-chain HK. The asserted references, either alone or in combination, to not teach or suggest the claimed method. For the reasons set forth above in connection with claim 16, the references fail to teach the use of HK, or any peptide thereof, as an anti-angiogenesis agent.

Reconsideration of the Section 103 rejection applied to claims 1-3, 8, 9, 16, 19 and 22 is respectfully requested.

Conclusion

The claims remaining in the application are believed in condition for allowance. An early action toward that end is earnestly solicited.

Respectfully submitted,

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